AMENDMENTS TO THE SPECIFICATION

Please amend the specification as follows:

In paragraph 21:

~~Certain~~ E[[e]]ndogenous peptides that exhibit~~have shown~~ antimicrobial activity against bacteria, fungi and enveloped viruses ~~but~~ with little or no cytolytic activity[[,]] have been isolated from diverse sources. Martin, E., et al., "*Defensins and other endogenous peptide antibiotics of vertebrates*," J. ~~of~~ Leukoc.~~yte~~ Biol.~~ogy~~ 58: 128-136[[,]] (1995). Most of these peptides share the property of being cationic but they differ considerably in other~~some~~ features[[,]] such as ~~their~~ size, the presence of disulfide bonds and structural motifs. Gabay, J.E., "*Ubiquitous Natural Antibiotics*," Science 264:373-374[[,]] (1994). These peptides have been shown to exert their antimicrobial activities either by forming multimeric pores in the lipid bilayer of the cell membrane or by~~through~~ interacting with macromolecular synthesis after penetration into the cell membrane. Zasloff, M., "*Antibiotic peptides as mediators of innate immunity*," Curr.~~ent~~ Opin.~~ions in~~ Immunol.~~ogy~~ 4: 3-7[[,]] (1992); see also Boman, H.G., et al., "*Mechanisms of action on Escherichia coli of cecropin P1 and PR-39, two antibacterial peptides from pig intestine*," Infect.~~ion and~~ Immun.~~ity~~ 61: 2978-2984[[,]] (1993). The most important aspect of antimicrobial peptides is that they rarely induce bacterial resistance. Oren, Z. and Shai, Y.~~, et al~~, "*A class of highly potent antibacterial peptides derived from pardaxin, a pore-forming peptide isolated from Moses sole fish Pardachirus marmoratus*," Eur.~~opean~~ J.~~ournal of~~ Biochem.~~istry~~ 237:[[,]] 303-310[[,]] (1996). Accordingly, antimicrobial peptides are promising candidates in the continuing search for a new class of antibiotics. It is an object of this invention to create antimicrobial peptides for use in antimicrobial treatments.

In paragraph 23:

The α-isoform of melanocyte-stimulating hormone (α-MSH) (SEQ. ID NO. 13) is a naturally occurring 13-amino acid peptide. α-MSH (~~SEQ. ID NO. 13~~) and its carboxy-terminal tripeptide, Lys-Pro-Val (SEQ. ID NO. 16), each have potent anti-inflammatory properties and ~~have~~ exhibit[[ed]] antimicrobial properties toward ~~two~~ representative ~~classes of organisms,~~ fungus and bacteria[[:]] (*S. aureus* and *Candida Albicans*,

respectively). Cutuli, M.~~Catania, A~~, et al., "*Antimicrobial Effects of alpha[[α]]-MSH Peptides*," J.~~ournal of~~ Leukoc.~~yte~~ Biol.~~ogy~~ 67: 233-239[[,]] (2000); see also, Lipton, J.M. and Catania, A., ~~et al.,~~ "*Anti-Inflammatory actions ~~Influence~~ of the Immunomodulator α-MSH*[[.]]," Immunol.~~ogy~~ Today 18: 140-45[[,]] (1997). The α-, β-, and γ-MSH peptides are derived from post-translation processing ~~and~~ of the precursor protein pro-opiomelanocortin. Pro-opiomelanocortin is expressed in the pituitary gland, in two brain areas ~~nuclei~~, and in several peripheral tissues. ~~Effects of~~ M[[m]]elanocortins have been shown ~~described~~ to effect ~~on~~ behavior, metabolism, fever, inflammation, analgesia, addiction, nerve regeneration, and the cardiovascular system. The presence of ~~the ancient anti-inflammatory~~ α-MSH ~~peptide α-melanocyte-stimulating hormone [α-MSH (1-13), SYSMEHFRWGKPV] (SEQ. ID NO. 13)~~ in barrier organs, such as gut and skin, suggests a role in nonspecific, or innate, host defense.

In paragraph 27:

In one preferred embodiment of the invention, a peptide is prepared that comprises R1-Lys-X1-Val (SEQ. ID NO. 1), where Val is the carboxy-terminal amino acid, ~~and~~ X1 is either Phe or DPhe, and ~~where~~ R1 is His-Phe-Arg-Trp-Gly. In another preferred embodiment of the invention, a peptide is prepared that comprises ~~contains~~ His-X2-Arg-Trp-Gly-Lys-Pro-Val (SEQ. ID NO. 2), where X2[[,]] is D[[-]]Phe[[,]] or DNal. A third peptide of the invention comprises ~~This can be combined with SEQ. ID NO. 1 via a Gly-Lys bond giving~~ His-X2-Arg-Trp-Gly-L[[s]]ys-X1-Val (SEQ. ID NO. 3). ~~Here, the sequences are connected through a Gly-Lys peptide bond resulting in a peptide where Val is the carboxy-terminal amino acid~~.

In paragraph 28:

In another preferred embodiment of the invention an octomeric peptide is prepared with a sequence R1-Lys-X3-Val (SEQ. ID NO. 4) wherein X3 is an amino acid bearing a non-polar functional group, and where Val is the carboxy-terminal amino acid. Non-polar functional group amino acids may be selected from the group consisting of ~~Gly,~~ Ala, Val, Leu, Ile, Met, Phe, Trp and ~~their~~ D-isomers thereof.

In paragraph 29:

In another preferred embodiment of the invention, a peptide is prepared that comprises R1-Lys-Pro-X4 (SEQ. ID NO. 5) where X4 is the carboxy-terminal amino acid and ~~where X4 bears~~ is an amino acid, not including Val, having a non-polar functional group, or a hydrophobic functional group. An amino acid having a h[[H]]ydrophobic functional group may be selected from the group consisting of Ala, DVal, Leu, Ile, Met, Pro, and ~~their~~ D-isomers thereof.

In paragraph 30:

In another preferred embodiment of the invention, a peptide is prepared that comprises R1-X5-Pro-Val (SEQ. ID NO. 6) wherein Val is the carboxy-terminal amino acid and where X5 is an amino acid~~, not including Lys,~~ having a non-polar functional group.

In paragraph 32:

In another preferred embodiment of the invention, a peptide is prepared consisting of R1-Lys-X7-Val (SEQ. ID NO. 8) where Val is the carboxy-terminal amino acid and where X7 is an amino acid having a negatively charged functional group. Negatively charged functional group amino acids may be selected from the group consisting of Asp, Glu, and ~~their~~ D-isomers thereof. In another preferred embodiment of the invention, a peptide is prepared where R1 of SEQ. ID NO. 7 is replaced with ~~SEQ. ID NO. 2,~~ His-X2-Arg-Trp-Gly~~-is connected to the Lys of SEQ. ID NO. 8~~, giving His-X2-Arg-Trp-Gly-Lys-X7-Val (SEQ. ID NO. 9), ~~and~~ where X2~~, as above,~~ is DPhe or DNal. ~~Similar to above, SEQ. ID NO. 2 and SEQ. ID NO. 7 are connected via a Gly-Lys.. In other words, SEQ. ID NO. 2 replaces the R1 in SEQ. ID NO. 7~~.

In paragraph 33:

In another preferred embodiment of the invention, a peptide is prepared comprising DTrp in position 4 giving His-Phe-Arg-DTrp-Gly-Lys-Pro-Val[[.]] (SEQ. ID NO. 10) where Val is the carboxy-terminal amino acid.

In paragraph 34:

In another preferred embodiment of the invention, a peptide is prepared comprising R1-Lys-X8-Val (SEQ. ID NO. 11) where Val is the carboxy-terminal amino acid and where X8 is an uncharged polar functional group ~~polar~~ amino acid.

Uncharged polar functional group amino acids may be selected from the group consisting of Asn, Gln, Ser, Thr and their D-isomers thereof.

In paragraph 35:

In another embodiment, a peptide is prepared where ~~comprising~~ His-X2-Arg-Trp-Gly replaces ~~(SEQ. ID NO. 2) connected through a Gly-Lys bond to~~ R1~~-Lys-X8-Val~~ of [[(]]SEQ. ID NO. 11[[)]] yielding His-X2-Arg-Trp-Gly-Lys-X8-Val (SEQ. ID NO. 12), ~~again,~~ where X2 is DPhe or DNal, X8 is an amino acid with an uncharged polar functional group, and ~~where~~ Val is the carboxy-terminal amino acid. ~~In other words, SEQ. ID NO. 2 has replaced the R1 in SEQ. ID NO. 11.~~

In paragraph 39:

Unmodified α-MSH (SEQ. ID NO. 13) is an ancient, thirteen amino-acid peptide produced by post-translational processing of the larger precursor molecule propiomelanocortin. The amino acid sequence of α-MSH is identical to amino acids ~~It shares the same~~ 1-13 of ~~amino acid sequence with~~ adrenocorticotropic hormone ([["]]ACTH[["]]) (SEQ. ID NO. 14), also derived from propiomelanocortin. α-MSH ~~(SEQ. ID NO. 13)~~ is secreted by many cell types, including pituitary cells, monocytes, melanocytes, and keratinocytes. It can be found in the skin of rats, in the human epidermis, or in the mucosal barrier of the gastrointestinal tract in intact and hypophysectomized rats. See e.g. Eberie, A. N., "*The Melanotrophins*," Karger, Basel, Switzerland (1998); Lipton, J.M. and Catania, A., ~~et al.,~~ "*Anti-inflammatory influence of the Neuroimmunomodulator α-MSH*," Immunol. Today 18, 140-145 (1997); Thody, A.J., et[[.]] al., "*MSH Peptides are Present in Mammalian Skin*," Peptides 4, 813-816~~815~~ (1983); Fox, J.A., et[[.]] al., "*Immunoreactive alpha* [[α-]]*Melanocyte Stimulating Hormone, Its Distribution in the Gastrointestinal Tract of Intact and Hypophysectomized Rats*," Life[[.]] Sci. 28~~18~~, 2127-2132 (1981).

In paragraph 40:

α-MSH ~~(SEQ. ID NO. 13)~~ and its derivatives are known to have potent antipyretic and anti-inflammatory properties, yet they have extremely low toxicity. They can reduce production of host cells' pro-inflammatory mediators *in vitro*, and can also reduce production of local and systemic reactions in animal models for inflammation.

The "core" α-MSH sequence Met-Glu-His-Phe-Arg-Trp-Gly (SEQ. ID NO. 15), for example, has learning and memory behavioral effects but little antipyretic and anti-inflammatory activity. In contrast, the active message sequence for the antipyretic and anti-inflammatory activities of α-MSH resides in the carboxy-terminal ~~amino acid~~ L[[l]]ys-P[[p]]ro-V[[v]]al sequence (SEQ. ID NO. 16) ~~of α-MSH~~. This tripeptide has activities *in vitro* and *in vivo* that parallel but are more potent than those of the parent molecule. The anti-inflammatory activity of α-MSH ~~(SEQ. ID NO. 13)~~ and/or its derivatives are disclosed in the following two patents which are hereby incorporated by reference: U.S. Patent No. 5,028,592, issued on July 2, 1991 to Lipton, J.M., entitled "ANTIPYRETIC AND ANTI-INFLAMMATORY PEPTIDES ~~LYS PRO VAL COMPOSITIONS AND METHOD OF USE~~;" U.S. Patent No. 5,157,023, issued on October 20, 1992 to Lipton, J.M., entitled "ANTIPYRETIC AND ANTI-INFLAMMATORY LYS PRO VAL COMPOSITIONS AND METHOD OF USE;" see also Catania, A. and Lipton, J.M., ~~et. al.~~, "*alpha[[α]]-Melanocyte Stimulating Hormone in the Modulation of Host Reactions*," Endocr. Rev. 14:[[,]] 564-576 (1993); Lipton, J.M. and Catania, A., ~~et.al.~~, "*Anti-inflammatory actions ~~influence~~ of the Neuroimmunomodulator of alpha[[α]]-MSH, ~~Immunol.~~*" Immunol. Today 18:[[,]] 140-145 (1997); Rajora, N., et[[.]] al., "*alpha[[α]]-MSH Production, Receptors, and Influence on Neopterin[[,]] in a Human Monocyte/macrophage Cell Line,*" ~~Line,~~ J. Leukoc. Biol. 59:[[,]] 248-253 (1996); Star, R.A., et[[.]] al., "*Evidence of Autocrine Modulation of Macrophage Nitric Oxide Synthase by alpha-melanocyte-stimulating hormone~~α-MSH~~*," Proc. Nat'l. Acad. Sci. (USA) 92:[[,]] 8016-8020 (1995); Lipton, J.M., et[[.]] al., "*Anti[[-]]inflammatory Effects of the Neuropeptide alpha[[α]]-MSH in Acute, Chronic, and Systemic inflammation*," Ann. N.Y. Acad. Sci 741:[[,]] 137-148 (1994); Rajora, N., et[[.]] al., "*alpha[[α]]-MSH Modulates Local and Circulating tumor Necrosis Factor-alpha [[α]] in Experimental Brain Inflammation*," J. Neurosci.[[,]] 17:[[,]] 2181-2186 (1997); Richards, D.B. and Lipton, J.M., ~~et. al.~~, "*Effect of alpha-MSH (11-13) (lysine-proline-valine) on Fever in the Rabbit*," Peptides 5:[[,]] 815-817 (1984); Hiltz, M. E. and Lipton, J.M., ~~et. al.~~, "*Anti[[-]]inflammatory Activity of a COOH-terminal Fragment of the Neuropeptide alpha[[α]]-MSH*," FASEB J. 3:[[,]] 2282-2284 (1989).

In paragraph 52:

The following examples demonstrate the ability ~~and application~~ of modified α-MSH ~~related~~ peptides to combat bacteria. Methods in microbiology, molecular biology, and cell culture used but not explicitly described in this disclosure have already been amply reported in the scientific literature. The peptides used in the following examples were prepared by solid-phase peptide synthesis and purified by reversed phase[[d]] high performance liquid chromatography.

In paragraph 56:

Table~~Figure~~ 1 shows that modified α-MSH peptides greatly reduced the ability of *C. albicans* to form colonies. This demonstrates that modified α-MSH peptides can inhibit the growth of *C. ~~andida~~ albicans*, an agent known to cause candidiasis, vaginitis, urethritis, balanoposthitis, and gastrointestinal infection in cancer patients. Bast, R.C. Jr., et al., "Cancer Medicine," 5th Ed., Hamilton:~~BC~~ Decker~~, Inc.~~, p. 157-163[[,]] (2000).

In paragraph 57:

Several of the~~The~~ modified α-MSH peptides disclosed herein not only retained their effectiveness, they[[,]] unexpectedly[[,]] were~~are~~ more potent inhibitors of *C. albicans* growth than~~relative to~~ naturally occurring α-MSH ~~(SEQ. ID NO. 13)~~or α-MSH (6-13), each of which inhibit[[ed]] *C. albicans* colony formation by less than 80%~~of the colonies~~. See U.S. Patent ~~Application~~ No. 6,800,291~~09/535,066~~, issued on October 5, 2004 to Lipton, J.M. and Catania, A.P., entitled "URO-GENITAL CONDITION TREATMENT SYSTEM." Applicants have designed modified α-MSH peptides and evaluated their antimicrobial activity ~~of modified α-MSH~~ toward *C. albicans*. These peptides were designed in part to determine the effect of the ~~sequence~~ Lys-Pro-Val (SEQ. ID NO. 16) and ~~on biological activity. The minimally active~~ His-Phe-Arg-Trp ~~sequence~~ (SEQ. ID NO. 17~~16~~) sequences on α-MSH biological activity ~~was chosen~~. The~~This~~ His-Phe-Arg-Trp sequence is important in interacting with melanocortin receptors, while the Lys-Pro-Val ~~(SEQ. ID NO. 15)~~ sequence is known to be important for antimicrobial activity. To determine~~In an attempt to elucidate~~ the contribution[[s]] of each ~~of the~~ amino acid[[s]] of the Lys-Pro-Val ~~(SEQ. ID NO. 16)~~ sequence toward antimicrobial activity, an alanine scan was performed. As shown in Table 1, the alanine

substitutions showeddisplayed that Lys and Pro are more important for antimicrobial activity than Val (compare results for SEQ. ID NOs. 19, 20, and 21) in activity. In contrast, rReplacing Val with DVal (SEQ. ID NO. 18) or, and with Leu[[,]] (SEQ. ID NO. 25) did not substantially alter antimicrobial activity, showing that this residue is not crucial. The importance of Val in the Lys-Pro-Val (SEQ. ID NO. 16) sequence is therefore unclear, and it maycould be a remnant of pro-opiomelanocortin biosynthesis.

In paragraph 58:

Replacing the Phe residue within the His-Phe-Arg-Trp sequence with DNal resulted in increased activity in many of thealmost all peptides tested (see results for SEQ. ID NO. 23; also, compare results for SEQ. ID NO. 27 vs. SEQ. ID NO. 20, SEQ. ID NO. 28 vs. SEQ. ID NO. 26, SEQ. ID NO. 32 vs. SEQ. ID NO. 31, SEQ. ID NO. 37 vs. SEQ. ID NO. 33, SEQ. ID NO. 42 vs. SEQ. ID NO. 39, SEQ. ID NO. 44 vs. SEQ. ID NO. 43, and SEQ. ID NO. 46 vs. SEQ. ID NO. 45), confirming a behavior found previously in melanocortin peptides.

In paragraph 59:

No substantial modification in activity was shown by SEQ. ID NO. 30 and SEQ. ID NO. 32, where Ser Replacingreplaced the Pro residue in the Lys-Pro-Val sequence with Ser resulted in a decrease in antimicrobial activity (see results for SEQ. ID NOs. 31 and 32). This decrease was more pronounced when Replacing the Pro residue was replaced from the Lys-Pro-Val sequence with either Asp (see results for SEQ. ID NO. 42) or Glu (see results for SEQ. ID NOs. 43 and 44)[[,]] resulted in decreased activity. TheseThis results confirm[[s]] earlier studies demonstrating that a negative charge in the carboxy-terminal region is deleterious to thefor antimicrobial activity of melanocortin peptides.

In paragraph 60:

Peptides bearing a replacement of the Pro residue from the Lys-Pro-Val sequence with either Phe (SEQ. ID NOs. 33, 35, and 37) or DPhe (SEQ. ID NOs. 34, 36, and 38)[[,]] exhibited potent antimicrobial activity towards *Candida albicans*.

In paragraph 63:

Recent reports indicate that the candidacidal effect of α-MSH is mediated through cAMP induction. Cutuli, M.~~Catania, A.~~, et al., "*Antimicrobial Effects of alpha[[α]]-MSH Peptides*," J.~~ournal of~~ Leukoc.~~yte~~ Biol.~~ogy~~ 67: 233-239[[,]] (2000). It is likely, therefore, that the modified α-MSH-related peptides enhance intracellular cAMP levels and thereby induce[[d]] toxicity.

In paragraph 64:

This example illustrates the generation of a novel peptide by modifying an α-MSH peptide (SEQ. ID NO. 13). SEQ. ID NO. 37 is used herein to illustrate~~chosen here for this example. This is a representative example of~~ how all of the peptide sequences in Table 1 were created. ~~By adding the desired amino acids during synthesis of the growing peptide chain, each of the peptide sequences can be generated.~~ All peptides were synthesized by solid-phase peptide synthesis followed by RP-HPLC purification.